HOW DOES UNDERLYING CARDIOPULMONARY DISEASE INFLUENCE RESPONSE TO PM IN ANIMALS?

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research and development

Introduction

- *"The moral test of a government is how it treats those who are at the dawn of life, the children; Those who are in the twilight of life, the aged; And those who are in the shadow of life, The sick, the needy and the handicapped." (Hubert Humphrey, 1976)*
- Epidemiological studies show that PM exposure increases mortality and morbidity, especially in elderly with cardiovascular and pulmonary diseases. However, these studies can provide only associations, and clinical studies are limited with ethical concerns, especially in frail individuals.
- Careful use of animal models with naturally occurring genetic predisposition, experimentally created genetic manipulations, and chemically or surgically induced diseases allow one to identify mechanisms and risk factors which predispose humans exacerbated injuries.

Research Goals

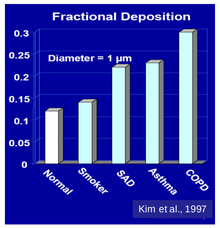
- Identify/develop animals models of human cardiovascular and chronic pulmonary diseases, and conduct PM studies in parallel to healthy models. Determine if susceptibility can be linked to humans, based on common biomarker evaluations.
- Investigate the roles of physiological and genetic factors, using genetic and experimentally created animal models. Investigate the role of common susceptibility factors, such as underlying oxidative stress.
- Investigate mechanisms of PM component-specific exacerbation of disease conditions. Identify the role of neurohumoral, and systemic factors in acute versus chronic PM health effects.
- Determine susceptibility in relation to disease progression. Develop integrated approaches which allow the use animal data to support human susceptibility.

Genetic and environmental interactions

Methods/Approach

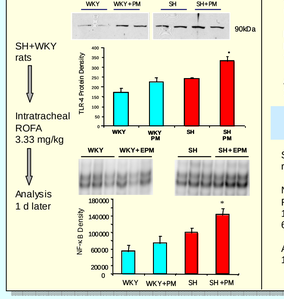
Animal Models
Cardiovascular Diseases Models
Spontaneously Hypertensive (SH) rats- genetic
Experimental MI
Apo E-/-
Pulmonary Disease Models
Asthma, Ova mice
ARDS-pulmonary vasculitis-MCT
Experimental COPD/bronchitis
Infections
PM Sources
Oil combustion-derived fugitive emissions, diesel, ambient collected, individual components, real time concentrated ambient PM, synthetic ultrafines
Health Outcomes
Cardiac and pulmonary physiology, systemic biomarkers, hematological and coagulation markers, vascular physiology, conventional and high-throughput gene and protein expressions, inflammation and oxidative stress markers, pathology

Underlying diseases affect particle deposition dose

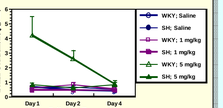


Spontaneously Hypertensive (SH) Rat as a Model of Genetic Cardiovascular Disease

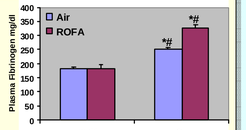
TOL-4 signaling demonstrate an active state in lungs of SH than in WKY rats; with PM exerting additional exacerbation



Greater oxidative stress in SH than in WKY rats following acute PM exposure

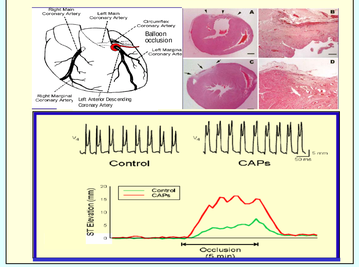


Fibrinogen increase in SH but not in WKY rats following inhalation of PM



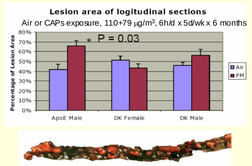
Experimental Myocardial Infarction: A Rat Model

ST segment elevation in CAPs exposed rats immediately following surgical MI



Mouse Model of Atherosclerosis (ApoE-/-)

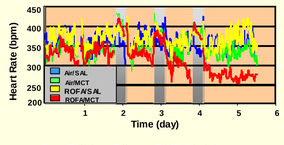
Increased vascular lesions in ApoE-/- but not wild-type mice



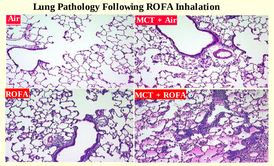
Pulmonary Vasculitis Model

Although with high concentrations of particles, underlying pulmonary vasculitis was associated with exacerbated cardiac impairments and pulmonary pathology

Heart rate changes following ROFA inhalation



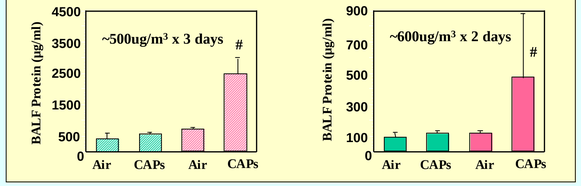
Lung Pathology Following ROFA Inhalation



ROFA Inhalation (15 mg/m³ x6h/d x3d): Monocrotaline-treated Rats (60 mg/kg, i.p.; exposure 10 d post

Rat Model of Sulfur Dioxide-Induced Bronchitis

Bronchitic rats demonstrate increased sensitivity to concentrated PM (CAPs)-induced inflammation



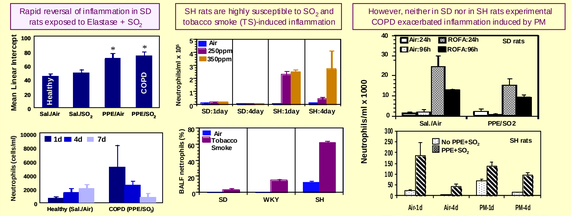
Chronic Obstructive Pulmonary Disease (COPD): Rat Models

Genetic differences determine variations in susceptibility to experimental COPD or PM-induced pulmonary impairments

Rapid reversal of inflammation in SD rats exposed to Elastase + SO_2

SH rats are highly susceptible to SO_2 and tobacco smoke (TS)-induced inflammation

However, neither in SD nor in SH rats experimental COPD exacerbated inflammation induced by PM



SD rats were instilled with PPE, 600 U/kg 2 wks prior to their exposure to SO_2 (250 ppm, 5 h/d x 5d/wk x 6 wks. One, 4 or 7 d following exposure BALF was analyzed for inflammation.

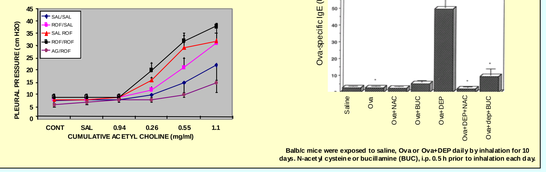
Upper: SD or SH rats were exposed to SO_2 (5 h/d x 4d. One, or 4 d following exposure BALF was analyzed for inflammation. Lower: SD, WKY or SH rats were exposed to ~90 mg/m3 ETS, 6h/d for 2 d. BALF was analyzed for inflammation 1 d later.

Upper: SD rats were exposed to PPE (600 U/kg, 2 wks prior to start SO_2. Then exposed to SO_2 (250 ppm, 5h/d x 5d/wk x 6 wks). One day later exposed to nose-only ROFA (10 mg/m3, 6h/d x 2 d). Lower: SH rats without or with PPE+SO2 were exposed to ROFA, nose-only, 20 mg/m3, 6h/d x 2 d.

Mouse Model of Allergic Asthma: Ovalbimin

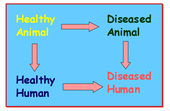
Rats exposed to residual oil fly ash increases airway reactivity during allergic sensitization to house dust mite allergen

Thiol antioxidants inhibit adjuvant effect of inhaled DEP



Balb/c mice were exposed to saline, Ova or Ova+DEP daily by inhalation for 10 days. N-acetyl cysteine or buciliamine (BUC), i.p. 0.5 h prior to inhalation each day.

Toxicological Paradigm for Use of Susceptible Disease Models



Future Directions

Continue investigating mechanisms of underlying diseases in exacerbation of component-specific PM effects on pulmonary and cardiovascular systems.

Delineate the roles of genetic versus physiological and environmental risk factors via use of transgenic, natural polygenic, and experimental models.

Provide linkage between human and animal models Using high through put genomic/proteomic approaches.

Investigate exacerbation due to acute versus long-term PM exposures focusing on host compensatory mechanisms.

The knowledge on genetic and environmental interactions in determining variations in susceptibility will improve our judgmental ability for determining risks of PM to most vulnerable populations.

Outcomes and Impact

To protect health of most susceptible individuals, we need to understand the mechanisms of variations in human susceptibilities. Epidemiological studies have demonstrated that PM exposure increases mortality and morbidity in individuals with cardiopulmonary diseases.

Our use of animal models demonstrate exacerbation of PM effects; and identify genetics, the existence of disease, and altered physiology as major risk factors. Although, more research is needed to identify specific genetic and epigenetic mechanisms.

Human susceptibility is an emerging biomedical field. The combination of genomic/proteomic approaches and animal models will provide mechanistic understanding of susceptibility.

The understanding of the genetic and environmental risk factors which predispose humans to increased susceptibility are essential in judging how much PM burden can be taken by those frails without increasing morbidity and mortality.

Health and Exposure